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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,240	06/26/2006	Atsushi Nakayama	292110US0PCT	3061
22850 7590 03/20/2009 OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C. 1940 DUKE STREET ALEXANDRIA, VA 22314				
EXAMINER HAYLIN, ROBERT H				
ART UNIT		PAPER NUMBER		
1626				
NOTIFICATION DATE		DELIVERY MODE		
03/20/2009		ELECTRONIC		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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# Office Action Summary

**Application No.**

10/584,240

**Applicant(s)**

NAKAYAMA ET AL.

**Examiner**

ROBERT HAVLIN

**Art Unit**

1626

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 22 December 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 8, 10-19 and 21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-7, 9 and 20 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/S508)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

**Status of the claims:** Claims 1-21 are currently pending.

**Priority:** This application is a 371 of PCT/JP04/19578 (12/27/2004) and claims foreign priority to JAPAN 2003-431680 (12/26/2003), JAPAN 2004-283082 (09/29/2004), JAPAN 2004-312335 (10/27/2004).

**IDS:** The IDS dated 11/26/07, 9/26/06, and 6/26/06 were considered.

### ***Election/Restrictions***

Applicant's election without traverse of Group II (claims 1-7, 9, and 20) in the reply filed on 12/22/08 is acknowledged. Applicant also elected the species of example 14. Because the generic claim 1 was found unpatentable, the provisional election of species is placed in effect and the claims are restricted to the elected species only and the subject matter not reading thereupon is withdrawn from consideration.

### ***Claim Rejections - 35 USC § 103***

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

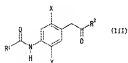
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
3. Claims 1-7, 9, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakayama et al. (WO 02/053534 (cited in the IDS as equivalent of US 2003/0134859, now US 7,157,487) published in Japanese on 07/11/2002, references below are to the English '487 patent) in view of March's Advanced Organic Chemistry, 5<sup>th</sup> ed., (2001) ("March").

The instant claims are for a process of producing a compound of formula III:



comprising reacting a compound of formula I ( $\text{R}^1\text{COO}^-\text{H}$ ) with a



chlorinating agent and a compound of formula II ( ) under acidic conditions without addition of a base.

1. *Determining the scope and contents of the prior art.*

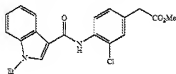
Nakayama teaches methods of synthesizing VLA-4 inhibitors. The reference teaches generic processes such as in scheme 1 where an amide bond is formed from in the presence of acid and utilizing acid halides such as oxalyl chloride. See cols. 49-51 and Scheme 1C.

Specifically, in col. 233 the reference teaches formation of an amide bond between 1-ethylindole-3-carboxylic acid and methyl-3-chloro-4-aminophenylacetate in the presence of oxalyl chloride:

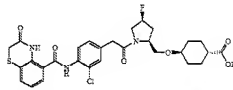
Example 90

trans-4-(1-(3-Chloro-4-((3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-5-yl-carbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid

(Step 5) Synthesis of methyl 3-chloro-4-((1-ethyl-3-indolyl-carbonyl)amino)phenylacetate



To 1-ethylindole-3-carboxylic acid (160.2 mg, 0.847 mmol) were added methylene chloride (3.5 ml) and oxalyl chloride (108.9  $\mu$ l, 1.270 mmol) under stirring at 15° C. The reaction mixture was stirred for 2.5 hours at room temperature. The solvent was then distilled off under reduced pressure. To the residue was added methylene chloride (3.5 ml). Under stirring at room temperature, a solution of methyl 3-chloro-4-aminophenylacetate (177.5 mg, 0.889 mmol) in methylene chloride (3.5 ml) and triethylamine (0.37 ml, 2.657 mmol) were added and the mixture was heated under reflux for 18 hours. After the reaction mixture was cooled to room temperature, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform. The resulting solution was washed with 1N HCl and saturated saline, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to give methyl 3-chloro-4-((1-ethyl-3-indolyl-carbonyl)amino)phenylacetate (277.7 mg, 88%) as a brown amorphous substance. The resulting compound was provided for the subsequent reaction without further purification.



A mixture of trans-4-(1-(4-amino-3-chlorophenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid (500  $\mu$ l of a 1.0M DMF solution, 0.50 mmol), 3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-5-carboxylic acid (105 mg, 0.5 mmol), HOBT (0.95 ml of a 1.0M DMF solution, 0.95 mmol), EDC HCl (1.5 ml of a 0.6M DMF/methylene chloride solution, 0.75 mmol) and DMAP (catalytic amount) was stirred in a screw vial for 18 hours at room temperature. The reaction mixture was diluted with chloroform (3 ml) and the diluted solution was poured in a fit syringe which had been pre-pelleted with acidic Hydro-matrix. The syringe was washed with chloroform. The solvent was distilled off and to the residue were added THF/methanol (4 ml, 3:1) and 1M NaOH. The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was distilled and the residue was purified by high-performance liquid chromatography (ARW system) to give the title compound (15 mg, 5%) as a colorless solid.

In col 294:

March teaches related well known methods of forming amides in a synthetic scheme and represents the depth of knowledge of those of ordinary skill in the art with respect to abilities to optimize reaction conditions, etc. In addition, the reference teaches reacting an acyl chlorides with an amine to form an amide bond. The reference also teaches the well known transformation of a nitro group to an amino group.

2. *Ascertaining the differences between the prior art and the claims at issue.*

The only apparent difference between the prior art and the claims is that the instant claims explicitly state the use of acidic conditions. However, when considering the elected species of example 14 the reaction conditions do not show a substantial difference from the prior art.

With respect to claim 2, a further difference is ethyl vs. methyl group on the indole. Claim 5 requires R2 is formula (a), while Nakayama teaches the related structure in example 90.

3. *Resolving the level of ordinary skill in the pertinent art.*

One of ordinary skill in the art of organic synthesis would be well versed in the teachings of references such as March. One of ordinary skill in the art would consider routine and well within their technical grasp the process of altering reaction conditions to maximize yield. In addition, those of ordinary skill in the art would first look to known synthetic methods in the art that share structural elements with the object of their endeavor.

4. *Considering objective evidence present in the application indicating obviousness or nonobviousness.*

One of ordinary skill in the art would be motivated to optimize yield of the products taught by Nakayama. Based on the teachings of March and Nakayama, one of ordinary skill in the art would be know how to utilize different reaction conditions including acidic. In addition, one of ordinary skill in the art would recognize how the synthetic methods would be equally applicable to compounds with a similar core structure on differing only by the variables such as R1 and R2. Those of ordinary skill routinely use the a variety of reaction conditions that are well within their technical grasp and are commonly interchanged in order to routinely optimize the reaction conditions to maximize yield, etc.

The Supreme Court stated in *KSR* "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill." *KSR Intern. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731 (2007).

Because varying reaction conditions is routinely employed in improving methods of making organic compounds similar to those claimed here, the application of the same technique is obvious. Therefore, **the claims are rejected.**

#### ***Claim Objections***

Claims 4-7, 9 and 20 are objected to for being in an improper multiply dependent form.

#### ***Conclusion***

The claims are not in condition for allowance.

#### ***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Havlin whose telephone number is (571) 272-9066. The examiner can normally be reached on Mon. - Fri., 7:30am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful the examiner's supervisor, Joe McKane can be reached at (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert Havlin/  
Examiner, Art Unit 1626

/Rebecca L Anderson/  
Primary Examiner, Art Unit 1626